RE: GENERAL EFFICACY OF WELLBUTRIN XL® FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

SUMMARY

- Wellbutrin XL® (bupropion HCl extended-release tablets) is a once-daily formulation of bupropion indicated for the treatment of major depressive disorder (MDD) in adults aged 18 and older.

- Studies have demonstrated similar bioavailability between *Wellbutrin XL* and Wellbutrin® (bupropion HCl) Tablets, the immediate-release formulation of bupropion and Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets, the sustained-release formulation of bupropion. Based on bioequivalence, *Wellbutrin XL* offers similar efficacy and tolerability as other formulations of bupropion.

- The efficacy of bupropion for the treatment of MDD was established with *Wellbutrin* in two 4-week, placebo-controlled trials in adult inpatients and in one 6-week trial in adult outpatients.

- The long-term (52-week) efficacy and safety for bupropion as maintenance treatment to prevent relapse/recurrence in depressed patients was established with *Wellbutrin SR*.

- The efficacy and safety of *Wellbutrin XL* for the treatment of MDD in patients with specific depressive symptoms of low energy, pleasure, and interest was evaluated in an 8-week placebo-controlled trial.

Some information contained in this response may be outside the approved Prescribing Information for *Wellbutrin XL*. This response is not intended to offer recommendations for administering *Wellbutrin XL* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Wellbutrin XL,* we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Wellbutrin XL*.

BACKGROUND

Bupropion, an antidepressant with dual neurotransmitter properties, is a norepinephrine and dopamine reuptake inhibitor (NDRI) (1). Bupropion has no clinically significant effect on serotonin neurotransmission and essentially no affinity for muscarinic, histaminergic, dopaminergic, or alpha-adrenergic receptors. Norepinephrine and dopamine are 2 of the neurotransmitters believed to be important in regulating mood (2). Norepinephrine, in addition to its effects on mood, is important in regulating anxiety (3).

CLINICAL INFORMATION

Studies have demonstrated similar bioavailability of the immediate-release and the extended-release formulations of bupropion under steady-state conditions (4). The bioavailability (both peak plasma concentration and extent of absorption) of *Wellbutrin XL* 300 mg once daily was similar to that of 100 mg 3 times daily of *Wellbutrin* for parent drug and metabolites. Similar studies have also demonstrated the bioequivalence of *Wellbutrin XL* and *Wellbutrin SR*. Based on bioequivalence, *Wellbutrin XL* offers similar efficacy and tolerability as other formulations of bupropion.

Wellbutrin

The efficacy of bupropion for the treatment of MDD was established with *Wellbutrin* in two 4-week, placebo-controlled trials in adult inpatients and in one 6-week, placebo-controlled trial in outpatients.

Depressed Adult Inpatients

A 28-day, double-blind, randomized, parallel-treatment, placebo-controlled multicenter trial was conducted in 75 depressed inpatients (5). Patients were required to be nonpsychotic adult inpatients (ages 18 to 70 years) admitted for the treatment of MDD. The use of psychotropic medications within 7 days prior to the start of the study was prohibited (14 days prior for a monoamine oxidase inhibitor [MAOI] or 28 days for an antipsychotic) with the exclusion of hypnotics. Patients were randomized to treatment with *Wellbutrin* (300 to 600 mg/day) or placebo. Efficacy measures included the Hamilton Rating Scale for Depression (HAMD), Hamilton Rating Scale for Anxiety (HAMA), Zung Self-Rating Depression Scale (SDS), Zung Self-Rating Anxiety Scale (SAS), and Clinical Global Impressions (CGI) scale. Safety was assessed by a 33-item side effect assessment scale.

Forty-eight patients who received *Wellbutrin* (300-600 mg/day in divided doses) and 27 patients who received placebo were included in the efficacy analysis. Seventy-eight percent (78%) of patients received maximum doses of 450 mg/day or less. The treatment period was 28 days, however, patients completing 21 days of treatment were eligible for the efficacy analysis.

By day 21, HAMD total scores were significantly reduced among patients receiving *Wellbutrin* compared with placebo ($P = 0.004$). The depressed mood item (item 1) from the HAMD and the CGI severity score was also improved among patients treated with *Wellbutrin* compared with placebo. *Wellbutrin* was significantly more effective than placebo in reducing depressive and anxious symptomatology, beginning at week 3 ($P < 0.05$). Symptoms reflecting cognitive disturbance, anxiety/somatization, and psychomotor retardation were significantly improved compared with placebo ($P < 0.05$).

Wellbutrin was generally well tolerated. Adverse events occurring more often in the *Wellbutrin* group included dry mouth, sweating, and increased motor activity, nausea/vomiting, weight loss, and weight gain occurred more frequently in the placebo group. Three patients receiving *Wellbutrin* reported a rash and treatment was discontinued in 1 patient. Cardiovascular measures (blood pressure, pulse, ECG) showed no clinically significant differences between placebo or bupropion. No seizures or other major adverse events were reported.

A second trial of similar design was conducted in 109 adult inpatients who were randomized to 1 of 3 treatment groups (*Wellbutrin* 300 mg/day, *Wellbutrin* 450 mg/day, or placebo) for 28-days (6). Efficacy (HAMD and CGI-S) and safety (physical examinations, vital signs, ECG, and adverse experiences) assessments were made at baseline and at weekly intervals throughout the study.

Statistically significant reductions on the HAMD, CGI-I, and CGI-S scales were reported on days 21 and 28 of treatment for patients receiving *Wellbutrin* compared with placebo ($P < 0.05$). Sixty-one percent (61%) of patients treated with *Wellbutrin* showed a 50% reduction in HAMD scores compared with 36% of placebo-treated patients ($P = 0.005$). The results were positive for the HAMD total score, but not for the HAMD item 1. The incidence of adverse events were similar for patients treated with placebo and *Wellbutrin.* Adverse events more common among the group treated with *Wellbutrin* were syncope, pruritis, excessive sweating, impaired sleep quality, tremor, and blurred vision. Thirteen percent (13%) of patients treated with *Wellbutrin* discontinued due to adverse events compared with none of the patients receiving placebo.

Depressed Adult Outpatients

A 6-week, 5-center, double-blind, randomized, placebo-controlled study was conducted in 216 depressed outpatients (7). Patients included in the study had to be at least 18 years old with a current major depressive episode lasting 4 weeks to 2 years and judged not to be secondary to a preexisting psychiatric or medical condition. In addition, HAMD total score had to be at least 20 at screening. The use of psychotropic medications within 7 days prior to the start of the study was prohibited (14 days prior for an MAOI or 28 days for an antipsychotic) with the exclusion of hypnotics. Patients were randomized to *Wellbutrin* 100 mg twice daily (BID) for the first 3 days, then 100 mg three times daily (TID) for the remainder of the study or placebo. Efficacy assessments included HAMD, Montgomery Asberg Depression Rating Scale (MADRS), CGI-I, and CGI-S. Safety was assessed by vital signs, weight, and adverse experiences.

Wellbutrin was effective based on the HAMD total score, HAMD item 1, MADRS, CGI severity score, and CGI improvement score ($P < 0.05$, LOCF). Statistically significant differences on the HAMD with *Wellbutrin* were observed as early as day 14 in 1 individual center analysis ($P < 0.10$, LOCF) and by day 28 in the combined analysis ($P < 0.05$, LOCF). Adverse events reported more often among patients treated with bupropion included headache, insomnia, dizziness, nausea, agitation, and constipation. No seizures or other major adverse events were reported. Six patients receiving *Wellbutrin* and 5 patients receiving placebo dropped out of the study due to adverse events. *Wellbutrin* was associated with significantly more weight loss than placebo ($P < 0.01$).

Wellbutrin SR

The antidepressant efficacy of *Wellbutrin SR* 150 mg once daily and 150 mg BID was evaluated in a multicenter, double-blind, placebo-controlled, fixed-dose trial (8). Following a 1-week placebo lead-in phase, outpatients with moderate to severe depression were randomized to receive *Wellbutrin SR* 150 mg once daily (n=121), *Wellbutrin SR* 150 mg BID (n=120), or placebo (n=121) for 8 weeks. Compared with placebo, improvements on the HAMD total score, CGI-S and CGI-I scores with *Wellbutrin SR* 150 mg/day were statistically significant ($P \leq 0.05$). Similarly, improvements on the HAMD total score, the HAMD depressed mood item, CGI-S and CGI-I with *Wellbutrin SR* 150 mg BID compared with placebo were statistically significant ($P \leq 0.05$). Efficacy for both dosages of *Wellbutrin SR* were comparable. Adverse events leading to discontinuation with *Wellbutrin SR* included skin conditions, mainly rash (n=8), agitation and insomnia (n=5), and nausea and constipation (n=4). Overall, headache was the most frequently reported adverse event (21.7%, 24.1%, and 18% for *Wellbutrin SR* 150 mg, *Wellbutrin SR* 300 mg, and placebo, respectively). More patients treated with *Wellbutrin SR* 300 mg compared with *Wellbutrin SR* 150 mg reported sweating (11.2% vs 4.2%) and constipation (10.3% vs 5%). A greater weight loss was observed with *Wellbutrin SR* 300 mg (1 kg) and *Wellbutrin SR* 150 mg (0.5 kg) than with placebo (0.2 kg).

The safety and efficacy of *Wellbutrin SR* was evaluated for relapse prevention of depression in adults (9). Patients had a diagnosis of moderate to severe, recurrent major depression, a minimum score of 18 on the HAMD, and a current depressive episode of between 8 weeks and 24 months duration. The use of psychotropic medications within 7 days prior to the start of the study was prohibited (14 days prior for an MAOI or protriptyline, 28 days for fluoxetine or any investigational drug). Patients were excluded from the study if they had a predisposition to seizures, were receiving medications that lowered the seizure threshold, had a history of anorexia or bulimia, had a DSM-IV Axis II diagnosis suggesting a propensity for noncompliance or nonresponsiveness to pharmacotherapy for depression, were actively suicidal, or were pregnant, lactating, or unwilling to avoid pregnancy during the study.

All patients (N= 816) received open-label treatment with *Wellbutrin SR* 150 mg BID for 8 weeks. Responders, based on a CGI-I score of 1 or 2, who wanted to continue the study were randomized in a

double-blind manner to *Wellbutrin SR* 150 mg BID (n = 210) or placebo (n = 213) for 44 weeks. Relapse was defined as the point in time when the investigator determined an intervention (drug prescription or electroconvulsive therapy) was necessary. This endpoint was chosen to more closely approximate the clinical practice setting.

Most patients (81%) had moderate depression. Of the 816 patients, 448 were responders and 423 continued onto the double-blind phase. Patients receiving *Wellbutrin SR* had a statistically significantly lower relapse rate over 12 months compared with patients taking placebo *(P* = 0.004). Median time to relapse was longer for the *Wellbutrin SR* (≥week 44) group as compared with the placebo group (week 24). The odds of placebo-treated patients needing treatment for relapse over 1 year was 1.83 times higher than for patients that received *Wellbutrin SR*. Kaplan Meier estimates indicated approximately half (52%) of patients on placebo would become depressed by the end of the study versus approximately one-third (37%) of patients on *Wellbutrin SR.*

Wellbutrin SR was well tolerated during long-term therapy. The most common adverse events during acute therapy were dry mouth, nausea, headache, and insomnia (Table 1). Most adverse events were transient. The percentages of patients that discontinued the study due to adverse events were 9% during the open-label phase and <1% and 4% for placebo and *Wellbutrin SR*, respectively during the double-blind phase. No clinically important changes in blood pressure, pulse rate, or laboratory assessments were found.

Table 1: Adverse Events Reported by at Least 5% of Patients and at a rate 1.5 times More Than Placebo (9)

Adverse Event Term	Adverse Events by Treatment Arm [n (%)]		
	Open-label *Wellbutrin SR* (N = 816)	**Double-blind Placebo (n=213)**	**Double-blind *Wellbutrin SR* (n=210)**
Headache	28	13	16
Dry mouth	26	0	<1
Insomnia	16	3	3
Nausea	13	2	4
Constipation	9	1	<1
Dizziness	9	3	<1
Agitation	8	1	<1
Infection	7	5	10
Tinnitus	7	<1	<1
Dyspepsia	6	3	5
Anorexia	6	<1	<1
Tremor	6	0	1
Rhinitis	3	4	7

The effect of time to response, time to remission, and the effect of residual depressive symptoms on relapse after 8 weeks of *Wellbutrin SR* treatment were determined in post-hoc analyses (10). The time to response was defined as the first week in which there was at least a 50% reduction in the HAMD. Remission was defined as a HAMD-17 score ≤6. Neither time to response nor time to remission were associated with relapse during the 44-week continuation phase. Likewise, the presence of continued symptoms at the end of open-label treatment was not related to relapse. However, responders within the first 2 weeks of treatment were more likely to be in full remission at 8 weeks than later responders.

The quality of life (QOL) and productivity of patients was also evaluated from data during the open-label phase (baseline to week 8) (11). The Quality of Life in Depression Scale (QLDS) assessed quality of life among 816 patients receiving at least 1 dose of *Wellbutrin SR* 300 mg/day. Productivity was determined by data obtained from 466 working patients during an interview that included missed work hours due to

depression, time spent being effective at work, frequency of reduced effectiveness due to depression (0 = never, 1 = rarely, 2 = sometimes, 3 = usually, 4 = always), and hours of overall productivity. Overall productivity loss was calculated from the sum of productivity lost from work absenteeism and productivity lost from reduced work effectiveness. Only patients who reported working full- or part-time were included in the analysis (466 of 816 patients). The mean QLDS scores improved significantly with *Wellbutrin SR* (18.98 ± 7.78 to 10.36 ± 9.68, $P < 0.001$). During the last week of treatment, patients lost 1.58 fewer hours from work, were 14.6% more effective on the job, had a decrease of 1.17 points on the scale of reduced work effectiveness, and had 6.37 fewer hours of overall lost productivity as compared with pretreatment values *(*$P < 0.001$ for each variable). Patients that reported a CGI-I score of "very much improved" or "much improved" (responders) to *Wellbutrin SR* during weeks 6-8 had greater improvements in both QOL and productivity than did nonresponders *(*$P < 0.001$). Both responders and nonresponders had similar baseline QLDS and productivity scores.

Wellbutrin XL

Wellbutrin XL and placebo were compared in a multicenter, parallel group, double-blind, randomized trial for the treatment of adult outpatients with a primary diagnosis of MDD with core depressive symptoms of decreased energy, pleasure, and interest (12). To be included in the study, patients were required to have a minimum score of 25 on the 30-item Inventory of Depressive Symptomatology-Self Report (IDS-SR_{30}), collected via interactive voice response (IVR) technology over a touchtone telephone. The 30-item IDS was developed to remedy deficiencies in the HAMD and MADRS (13, 14, 15, 16). A primary advantage of the IDS is that, unlike the HAMD and MADRS, it rates all 9 of the criterion symptom domains needed to diagnose a major depressive episode. The 2 versions of the IDS, clinician administered (IDS-C_{30}) and self-report (IDS-SR_{30}) contain identical items, are highly correlated with each other and with the HAMD-17, and are sensitive to symptom changes associated with medication and psychotherapy. A version of the IDS-SR was developed for this study to allow self-report data to be collected by IVR. A minimum score of 1 on at least 4 of the 5 items and a minimum total score of 7 on the 5-item subscale of the IDS-SR_{30} that measured energy, pleasure, and interest was required for study inclusion.

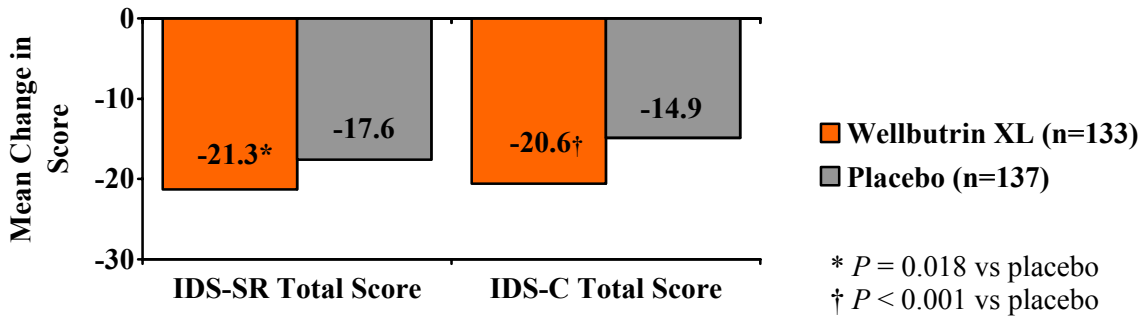
All subjects entered a 1-week screening phase. This phase was used to ensure that subjects meet all inclusion and exclusion criteria, including those related to laboratory evaluation, ECG evaluation, and had stable depressive symptoms. Subjects who exhibited greater than 25% change (either increase or decrease) in the IDS-SR from the screening to randomization visit were excluded. Patients were randomized to *Wellbutrin XL* or placebo. Patients received *Wellbutrin XL* 150 mg for the first week, 300 mg once-daily for the next 3 weeks and could be increased to 450 mg if inadequate clinical improvement was determined by the investigator. The 450 mg/day dose was given either in a single dose (300 mg + 150 mg in the morning) or, at the discretion of the investigator, as a split dose (300 mg AM dose followed 8 hours later by 150 mg dose). Any subject unable to tolerate the minimum dose of 300 mg/day was allowed to have the dose decreased to 150 mg/day once during the study. They were then required to increase the dose back to 300 mg/day after 1-2 weeks for the remainder of the study; subjects unable to tolerate 300 mg/day dose were discontinued from the study. Any subject unable to tolerate 450 mg/day were able to have the dose decreased to 300 mg/day for the reminder of the study. Clinic visits were scheduled for baseline and Weeks 1, 2, 4, 6, and 8.

The primary objective of the study was to compare the effectiveness of *Wellbutrin XL* versus placebo in for the treatment of MDD with core depressive symptoms of decreased energy, pleasure, and interest as measured by the IDS-SR_{30}. Secondary objectives included a comparison of efficacy based on the IDS-C_{30}; the IDS-SR_{30} subscale measuring symptoms of energy, pleasure, and interest; the 3-item IDS-SR_{30} subscale measuring insomnia; the X item IDS-SR_{30} subscale measuring anxiety symptoms; response rates measures by the IDS-$SR_{30,}$ the IDS-C_{30}, and the CGI-I; remission rates as measured by the IDS-SR_{30}, and

the IDS-C_{30};.effect on chronic pain as measured by the Pain Assessment Scale; and the effect on the CGI-S and CGI-I score.

A total of 274 subjects were randomized to receive *Wellbutrin XL* (n=135) or placebo (n=139). Significant improvements for the IDS-SR_{30} ($P = 0.018$) and IDS-C_{30} ($P < 0.001$) were observed with *Wellbutrin XL* compared with placebo at week 8 using last observation carried forward (LOCF) (Figure 1). Mean change in score for the 5-item subscale of the IDS-SR_{30} assessing energy, pleasure and interest was also significant with W*ellbutrin XL* (-6.7) compared with placebo (-5.3) ($P = 0.007$). Response was defined as a >50% reduction in IDS-SR_{30} and IDS-C_{30} scores, and based on CGI-I criteria, responders were defined as patients with a score of "much" or "very much" improved at study exit. Remission as a score ≤15 on the IDS-SR_{30} and ≤13 on the IDS-C_{30}. Response rates derived from the IDS-C_{30} and CGI-I scales were significantly greater for *Wellbutrin XL* at week 8. The IDS-C_{30} response rate for the group treated with *Wellbutrin XL* was 50% versus 35% for the placebo group ($P = 0.009$). The CGI-I response rates were 53% with *Wellbutrin XL* and 38% with placebo ($P = 0.006$). Although the response rate on the IDS-IVR_{30} for the *Wellbutrin XL* group (53%) was numerically higher than for the placebo group (45%), this trend did not reach statistical significance ($P = 0.084$). Remission rates were 41% with *Wellbutrin XL* and 27% with placebo based on IDS-SR_{30} ($P = 0.01$).

Figure 1: Change in IDS-SR and IDS-C Total Score with *Wellbutrin XL* and Placebo (LOCF) (12)



During the treatment phase, the percentage of patients who reported at least 1 adverse event (AE) was greater in the bupropion XL group (79%) than in the placebo group (61%). No serious adverse events or deaths were reported in either treatment group. Discontinuations due to adverse events was 9% with *Wellbutrin XL* and 2% with placebo. There were no reports of suicide, suicidal ideation, self-mutilation, or intentional self-injury in either treatment group. Patients treated with *Wellbutrin XL* lost more weight than patients treated with placebo over the 8 weeks (-3.04 lbs versus +0.37 lbs). Clinically significant changes in vital signs were observed for systolic blood pressure (10% and 9%), diastolic blood pressure (11% and 8%), and heart rate (<1% and <1%) for *Wellbutrin XL* and placebo, respectively. Table 2 lists adverse events reported in at least 5% of patients and at a rate 1.5 times that of placebo.

Table 2: Adverse Events Reported by at Least 5% of Patients and 1.5 times that of Placebo (12)

Adverse Event Term	Adverse Events by Treatment Arm [n (%)]	
	Placebo (n=139)	*Wellbutrin XL*(n=135)
Dry mouth	8 (6%)	17 (13%)
Dizziness	3 (2%)	14 (10%)
Nausea	7 (5%)	14 (10%)
Insomnia	2 (1%)	11 (8%)
Anxiety	1 (<1%)	8 (6%)
Dyspepsia	0	8 (6%)
Sinusitis	3 (2%)	7 (5%)
Tremor	0	7 (5%)

Quality of life parameters and effects on motivation and energy were also evaluated during this study (17). The Quality of Life Enjoyment and Satisfaction short form (Q-LES-Q-SF) and the Motivation and Energy Inventory (MEI) were the assessment tools utilized. The mean change in Q-LES-Q-SF was greater with *Wellbutrin XL* compared with placebo at week 8 for the observed (26 vs. 18.7, respectively, $P = 0.003$) and LOCF (21.5 vs. 15.2, respectively, $P = 0.004$) analyses. The mean change from randomization in MEI total scores for the *Wellbutrin XL* group was significantly greater than that of the placebo group at week 8 for the observed ($P < 0.001$) and LOCF ($P = 0.003$) analyses

REV0605

REFERENCES

1. Ferris RM, Cooper BR. Mechanism of antidepressant activity of bupropion. J Clin Psychiatry Monograph 1993;11:2-14.

2. Stahl SM. *Essential Psychopharmacology; Neuroscientific Basis and Practical Applications*. Cambridge, United Kingdom: Cambridge University Press; 1996:99-130, 167-195, 216-223, 249-262.

3. Foote SL, Aston-Jones GS. Pharmacology and physiology of central noradrenergic systems. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press Ltd; 1995:335-345.

4. Prescribing Information for *Wellbutrin XL*.

5. Fabre LF, Brodie KH, Garver D et al. Multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. J Clin Psychiatry 1983;44:88-94.*

6. Data on File, *Wellbutrin*, THRS/85/0038, Study 25 Clinical Study Synopsis, 1985.

7. Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. J Clin Psychiatry 1990;51:194-199.*

8. Reimherr FW, Cunningham LA, Batey SR, et al. A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. Clin Ther 1998;20:505-516. 203*

9. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. Biol Psychiatry 2002;51:753-761. AK1A4004*

10. Zisook S, Haight B, Bolden-Watson C, et al. Are time to response and degree of response during acute treatment with bupropion SR related to longer-term relapse? Poster presented at the 155th Annual Meeting of the American Psychiatric Association; May 18-24, 2002; Philadelphia, PA.

11. Dunner D, et al. Improved health-related quality of life and reduced productivity loss after treatment with bupropion sustained release: a study in patients with major depression. Primary Care Companion J Clin Psychiatry 2001;3:10-16.

12. Rush AJ, Wightman DS, VanMeter SA, et al. Wellbutrin XL for the treatment of adults with major depressive disorder. Poster presented at the 158th Annual Meeting of the American Psychiatric Association; May 22-26, 2005; Atlanta, GA. AK130931*

13. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res. 1986;18:65-87.

14. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med. 1996;26:477-86.

15. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003;54:573-83.

16. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. 2004;34:73-82.

17. Nelson C, Wightman DS, VanMeter SA, et al. Impact on energy and quality of life following treatment with once daily Bupropion XL for Major Depressive Disorder. Presented at: 45th Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting; June 6-9, 2005; Boca Raton, FL. AK130931

Enclosure: Prescribing Information for *Wellbutrin XL*